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Noninvasive photoacoustic measurement of the composite indicator dilution curve for cardiac output estimation

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Abstract: Recently, the measurement of indicator dilution curves using a photoacoustic (PA) technology was reported, which showed promising results on the noninvasive estimation of cardiac output (CO) that is an important hemodynamic parameter useful in various clinical situations. However, in clinical practice, measuring PA indicator dilution curves from an arterial blood vessel requires an ultrasound transducer array capable of focusing on the targeted artery. This causes several challenges on the clinical translation of the PA indicator dilution method, such as high sensor cost and complexity. In this paper, we theoretically derived that a composite PA indicator dilution curve simultaneously measured from both arterial and venous blood vessels can be used to estimate CO correctly. The *ex-vivo* and *in-vivo* experimental results with a flat ultrasound transducer verified the developed theory. We believe this new concept would overcome the main challenges on the clinical translation of the noninvasive PA indicator dilution technology.

OCIS codes: (170.0170) Medical optics and biotechnology; (170.3890) Medical optics instrumentation; (170.5120) Photoacoustic imaging; (170.4580) Optical diagnostics for medicine; (170.3880) Medical and biological imaging.

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1. Introduction

Photoacoustic (PA) technology is an emerging hybrid imaging modality that holds significant promises in noninvasive biomedical applications [1–4]. In this technology, an ultrasound signal is generated due to a photo-thermo-elastic effect when photons are absorbed by an absorbing medium, such as hemoglobin in tissue beds. As a result, the PA method enables to noninvasively acquire images and/or signals in biological tissues with an optical contrast and ultrasound resolution. These unique features open the door for numerous biomedical applications associated with, for example, breast cancer, total hemoglobin concentration, vessel specific oxygen saturation, just name a few.

Cardiac output (CO), the blood volume pumped out by the heart per minute, is an important physiological parameter that enables physicians to optimize fluid status in hemodynamically-instable and/or critically-ill patients [5–7]. For estimation of the CO in a clinical situation, indicator dilution methods have been widely used [5–9]. However, most of available indicator dilution methods are highly invasive. For the example of thermo-dilution [8–10], a bolus of low-temperature isotonic saline is injected as an indicator into the right atrium through a central venous catheter. The injected coldness is thermally diluted by blood flowing through the cardiovascular system. As the indicator is washed out of the system, a thermo-dilution curve is invasively measured with a temperature sensor located at the distal port of a pulmonary artery catheter [8] or a femoral arterial catheter [9,10], which is used to estimate CO. These highly invasive methods are complicated, could result in infections, and require trained medical professionals to use them. Therefore, there has been an increasing need for noninvasively assessing CO on critically-ill patients [11].

Recently, we introduced the concept of the noninvasive PA measurement of indicator dilution, and experimentally demonstrated its feasibility of estimating CO with the phantom mimicking cardiovascular circulation [12]. In this study, a bolus of room-temperature isotonic saline was used as the indicator, which induces a transient hemodilution effect in the porcine blood flowing in the phantom circulation system. This transient hemoduilution effect was noninvasively measured with a PA system on the downstream silicone tube that simulated an arterial blood vessel. To apply this PA CO measurement technology for a clinical situation, where a targeted peripheral artery is buried in tissue beds without knowing the exact depth and location, it is required to use a PA system with the functionality of auto-focusing and

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high imaging resolution, which is typically afforded with an ultrasound array detector [13]. As a result, the PA sensor for the clinical translation of this technology may be expensive, bulky, and complicated.

In this paper, we introduce an advanced method of the PA indicator dilution measurement, where indicator dilution signals from both an artery and its nearby vein are simultaneously measured by a simple flat ultrasound transducer, yielding a composite PA dilution curve, which could overcome clinical challenges described above. The validity of this advanced method for estimating CO accurately is theoretically verified and experimentally demonstrated with the phantom system mimicking cardiovascular circulation. Also, for the clinical feasibility of the composite PA indicator dilution method, CO estimation from composite PA indicator dilution curves of a live piglet measured with flat PA sensors will be presented.

2. Theoretical development

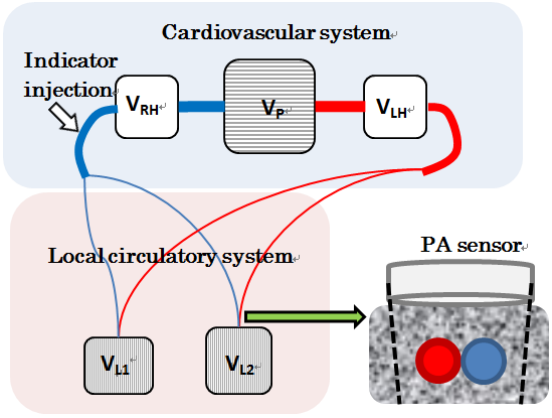

Fig. 1. The simple scheme of PA indicator dilution measurements with a flat ultrasound transducer is shown. V_{RH}: right atrium, V_P: vascular volume for right, left ventricles, and pulmonary blood vessels, V_{LH}: left atrium, and V_L: capillaries in the local circulatory system. For a PA indicator dilution curve, both the artery (red circle) and vein (blue circle) are measured by the PA sensor.

Figure 1 shows the scheme of the PA indicator dilution measurement in a clinical situation, where cardiovascular and peripheral circulatory systems are shown in blue and red transparent boxes, respectively. The terms, V_{RH}, V_P, and V_{LH} indicate a right atrium, cardiovascular volume containing ventricles and pulmonary blood vessels, and left atrium of the heart, respectively. Also, the term, V_{L1} and V_{L2} indicate local peripheral vascular volumes containing capillary structures. For estimating CO in a patient, a room-temperature isotonic solution indicator is instantaneously injected into the right atrium, which dilutes the blood in the cardiovascular system. The temporal variation of the indicator concentration is then measured from a downstream peripheral blood vessel as the indicator is washed out of the system. Typically, the peripheral arteries targeted for this indicator dilution method are adjacent to veins.

As shown in Fig. 1, a flat or near flat (i.e., very small numerical aperture) ultrasound transducer can be used to measure a composite indicator dilution curve generated from both artery and vein. In principle, the injected indicator passes through the peripheral artery under the detector, generating a PA indicator dilution curve from the artery, and then as it returns through its nearby vein, a secondary PA indicator dilution curve is generated from the vein. Because of many capillaries on the local vascular system, the indicator dilution in the vein is further diffused. In most clinical situations, the typical time delay between peripheral artery and vein indicator dilution curves is almost consistent with the duration of dilution curves

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[14,15] As a result, the measured composite dilution curve is the superposition of the curves from the artery and vein.

Since a PA signal from a blood vessel is approximately proportional to a hemoglobin concentration with a fixed oxygen saturation level [4,14], the mixed PA indicator dilution curve, $PA(t)$ measured by the PA sensor in Fig. 1 can be expressed as

$$PA(t) = \mathrm{K}_A \frac{tHb_A(t)}{\Delta V} + \mathrm{K}_V \frac{tHb_V(t)}{\Delta V} + PA_0, \tag{1}$$

where ΔV is the total blood volume passed at each PA measurement site during a fixed measurement interval, and $tHb(t)$ indicates the total hemoglobin (i.e., oxy- and deoxy-hemoglobin) contained in ΔV. The term K indicates a PA systematic factor converting the hemoglobin concentration (i.e., absorption coefficient) to the PA signal, which includes effects of a light source, optical properties of a background tissue bed, response function of an ultrasound transducer, etc. For all terms, the subscripts A and V indicate an artery and vein, respectively. It is known that an oxygen saturation level is different between arterial and venous blood, so the different terminologies for total hemoglobin are used in Eq. (1). Also, the PA systematic factor, K is notated differently for an artery and vein because PA-generating conditions of these two blood vessels, such as a vessel wall thickness, light fluence, etc., are different in general. The term, PA_0 represents all PA signals from PA sources that are insensitive to indicator dilution, such as ones from blood vessel walls and non-blood vessel absorbing tissue structures. Based on Eq. (1), the baseline PA signal before circulatory blood is diluted by the injected indicator is

$$PA_b = \mathrm{K}_A \frac{tHb_{b,A}}{\Delta V} + \mathrm{K}_V \frac{tHb_{b,V}}{\Delta V} + PA_0, \tag{2}$$

which can be assumed to be constant except the measurement noise.

Conceptually, the indicator (i.e., isotonic solution)-mixed blood can be divided into two portions of the pure isotonic solution and blood. Since the hemoglobin concentration in pure blood is invariant before and after the injection, it can be written

$$\frac{tHb_{b,A(V)}}{\Delta V} = \frac{tHb_{A(V)}(t)}{\Delta V - \Delta V_{I,A(V)}(t)}, \tag{3}$$

where $\Delta V_{I,A(V)}(t)$ is the volume of an indicator contained in ΔV. With the help of Eq. (2), substituting Eq. (3) to Eq. (1) results in

$$PA(t) = PA_b - \mathrm{K}_A \frac{tHb_{b,A}}{\Delta V} c_{I,A}(t) - \mathrm{K}_V \frac{tHb_{b,V}}{\Delta V} c_{I,V}(t), \tag{4}$$

where $c_{I,A(V)}(t) \equiv \Delta V_{I,A(V)}(t)/\ \Delta V$, indicator concentrations in the arterial and venous blood flows, respectively. Equation (4) shows that the PA signal generated from indicator diluted blood vessels is decreased from the background signal level. Because the indicator injected into an intravascular system doesn't interact with extravascular sites, and it could be assumed there is no blood reservoir (or, stagnant pool), like the heart, in a local circulatory system, the local circulatory system can be considered as a linear system in terms of indicator dilution [5]. Thus, the indicator concentration on the vein could be mathematically expressed as

$$c_{I,V}(t) = \int c_{I,A}(t')\, pr_L(t', t) dt', \tag{5}$$

where the indicator transfer point response function, $pr_L(t',t)$ represents the probability density function of an infinitesimal indicator in the artery to the vein. The simpler form of Eq. (5) is

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the convolution between $c_{I,A}(t')$ and $pr_L(t',t)$, but Eq. (5) is more general. Although there are capillary volumes in the local circulatory system, Eq. (5) is still valid as long as the vascular system is assumed to be linear in indicator dilution from the artery to vein with the constant CO [5,15].

With V_I amount of an instantaneously injected indicator, CO can be defined as [5,7–10]

$$CO \equiv V_I \Big/ \int_{-\infty}^{\infty} c_I(t)\,dt, = V_I \Big/ \mathrm{F}_{\sigma=0}\left[c_I(t)\right], \tag{6}$$

where $c_I(t)$ is an indicator concentration function and F_σ indicates Fourier transforming with the transformation variable of σ. For a conventional indicator dilution concept, $c_I(t)$ in Eq. (6) is typically measured from a single arterial blood vessel. But it will be mathematically verified that a composite PA indicator dilution can estimate CO. With the definition of CO in Eq. (6), Fourier transforming both sides of Eq. (4) with $\sigma = 0$ leads

$$\mathrm{F}_{\sigma=0}\left[PA_b - PA(t)\right] = \mathrm{F}_{\sigma=0}\left[c_{I,A}(t)\right]\left(\mathrm{K}_A \frac{tHb_{b,A}}{\Delta V} + \mathrm{K}_V \frac{tHb_{b,V}}{\Delta V}\right), \tag{7}$$

where Fourier transforming Eq. (5) with that $pr_L(t',t)$ is real and unit norm is applied to the procedure of Eq. (7). Also, it is assumed that the CO and hemoglobin concentrations in both artery and vein are remained as constant during the measurement of PA indicator dilution curves. Considering Eq. (2), Eq. (7) can be further developed to

$$\mathrm{F}_{\sigma=0}\left[c_{I,A}(t)\right] = \mathrm{F}_{\sigma=0}\left[PA_b - PA(t)\right] \Big/ \left(PA_b - PA_0\right). \tag{8}$$

Substituting Eq. (8) to Eq. (6) can derive the algorithm of estimating CO, which is

$$CO = \alpha \cdot V_I \Big/ \int_{-\infty}^{\infty} \left[1 - \frac{PA(t)}{PA_b}\right] dt, \tag{9}$$

where

$$\alpha = \left[PA_b - PA_0\right] \Big/ PA_b. \tag{10}$$

The result indicates that the PA indicator dilution curve measured from a mixture of an artery and vein using a simple, unfocused, and flat ultrasound transducer can be used to estimate CO.

3. Experimental results with discussion

To verify the proposed methodology, we performed *ex-vivo* experiments in a bench-top porcine blood circulation system and a pulsed laser diode equipped PA system. The detailed experimental setup and PA system parameters can be found elsewhere [12]. As the PA measurement site shown in Fig. 1, porcine looping tubes mimicking an artery and vein were contacted each other for composite PA indicator dilution measurements. The inner and outer diameters of the silicone tubes are 1.47mm and 1.91mm, respectively. The ultrasound transducer with the central frequency of 1MHz and the focal length of 0.8″ was roughly positioned without precise adjusting and focusing to measure PA signals generated from those two pig blood tubes. Because the purpose of the bench-top experiment is to verify the concept of a composite PA indicator dilution for the estimation of blood flows, water was used as the ultrasound coupling medium between the transducer and tubes instead of using a scattering medium.

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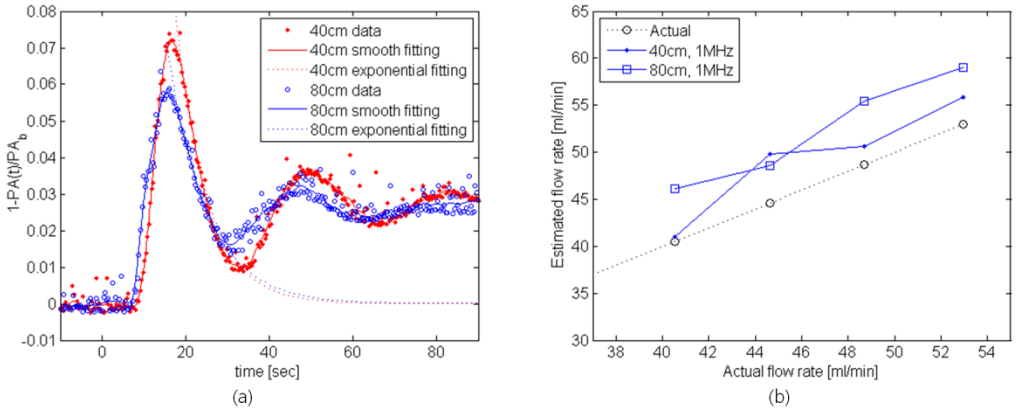

Fig. 2. (a) Experimentally measured normalized indicator dilution curves for 40cm and 80cm tube loop lengths between artery and vein measurement points when the flow rate is set to 52.5ml/min. (b) Estimated porcine blood flow rates using the algorithm of Eq. (9) with $\alpha = 1$.

Figure 2(a) shows normalized indicator dilution curves, 1- $PA(t)/PA_b$ calculated from experimentally measured composite PA indicator dilutions when the actual porcine blood flow was 52.5ml/minute. Notice that both $PA(t)$ and PA_b are PA signals simultaneously measured from both arterial and venous tubes. The lengths of the loop tubing between the arterial and vein contact points were set to 40cm and 80cm, respectively, to mimic different local circulatory vascular distances. As similar to indicator dilution curves acquired from a single artery [12], the tail of 1- $PA(t)/PA_b$ is typically contaminated by multiple circulations of the indicator. The area under 1- $PA(t)/PA_b$ without the recirculation is equivalent to the denominator of Eq. (9), which can be estimated by an conventionally used exponential fitting method [15]. The results of exponential fitting are indicated as the dotted lines in Fig. 2(a).

Figure 2(b) shows the estimated CO values (i.e., blood flow rates) using the algorithm of Eq. (9) with $\alpha = 1$ by assuming $PA_b >> PA_0$. Although the estimated CO values in Fig. 2(b) are slightly over-estimated, the overall trends are in a good agreement with that of actual flow rates. The over-estimation might be partially caused by non-zero PA_0, which implies $\alpha<1$ in Eq. (9) for accurately estimating CO. Figure 2(b) also shows that the amount of the over-estimation is higher for the 80cm loop tubing than the 40cm. It is reasonable to consider that for the 80cm loop tubing, the indicator concentration in the venous tube, $c_{I,V}(t)$ becomes more diffused and broader than that for the 40cm. This can be observed in Fig. 2(a), where the peak (valley) value of 1- $PA(t)/PA_b$ for the 80cm tube is lower (higher) than that for the 40cm tube. However, if the linearity of Eq. (5) is still valid for even such the broader $c_{I,V}(t)$, there must be little difference between the results of 40cm and 80cm loop tubing cases, as anticipated in the theory.

The reason for the higher over-estimation for the 80cm tube setup can be conjectured that the indicator transfer process from the artery to vein tubes deviates from the linear assumption of Eq. (5) much more than the 40cm tube case because the time difference between the arterial and venous dilutions for the 80cm tube is more than 6 seconds even with the fastest flow speed in the setup (52.5ml/minute) [16]. In a clinical situation, the typical time difference between arterial and venous dilutions is from a few to a few tens of seconds greatly depending on local circulatory systems and actual CO [17,18]. Therefore, it can be stated that the over-estimation caused by the nonlinearity of the indicator transfer process could be minimized from the selection of local circulatory systems. However, further investigation with clinical pilot studies is necessary to elucidate the phenomenon of the over-estimation, which leads to more accurate clinical estimation of CO.

As previously discussed [12], it is problematic to exactly measure the amount of PA_0, thus α, which adversely affects the estimation of CO, as shown in Eq. (9). For a non-clinical

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situation where measurement conditions are relatively stable, α could be approximated to 1 by increasing PA_b much larger than PA_0 with a focused PA sensor. In a clinical situation where there are various physiological noise factors, such as a respiratory motion, heartbeat, etc., however, the variation of α would be unpredictable and large unless the focused PA sensor could track the targeted artery in real time, which is another obstacle for the clinical translation of the PA indicator dilution method. For the newly suggested idea introduced in this paper, we anticipate PA_b is inherently increased by capturing two entire blood vessels altogether as the PA object.

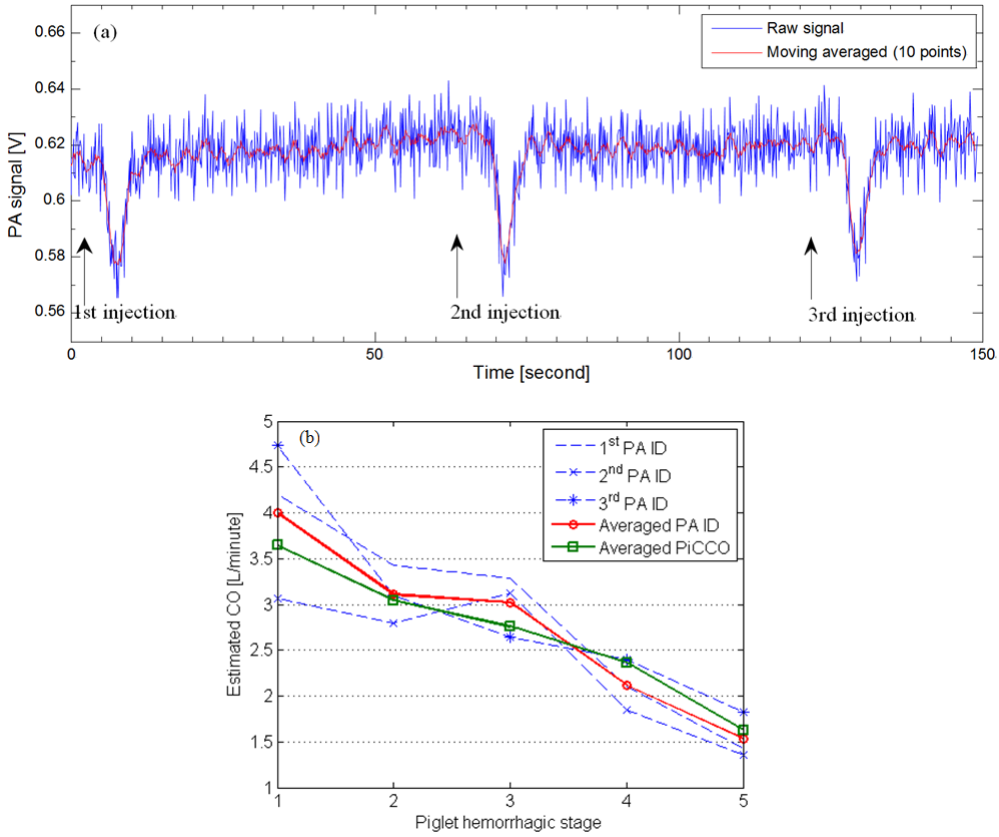

Fig. 3. Representative *in-vivo* PA CO measurement results for a live piglet. (a) *In-vivo* PA signal with a flat PA sensor with three consecutive indicator injections. (b) Estimated CO results: red line with open circles and green line with open squares are averaged CO values estimated from the PA ID method and PiCCO^{TM} reference, respectively.

To further investigate the feasibility of the proposed composite PA indicator dilution method for a clinical situation, we've performed *in-vivo* experiments with live piglets. In this experiment, the CO of the piglets was controlled by applying a hemorrhagic shock method [19], and the commercially available transpulmonary thermo-dilution device named PiCCO^{TM} was used for CO references [20]. In order to measure composite PA indicator dilution curves, a PA sensing system was prototyped by using two 905 nm pulsed laser diodes (OSI Laser Diode Inc.: CVN 5S63) and a 3.5 MHz flat ultrasound transducer (Blatek, 3.5MHz, −6dB bandwidth 82%). The PA sensor was placed over the saphenous artery and vein of the piglet, located about 3 mm below the tissue surface as verified with an ultrasound imaging system. As usually conducted in clinical CO diagnoses, three consecutive measurements were performed for each piglet hemorrhagic CO plateau, and the average of each set of three

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measurements was used as the final result. Figure 3 shows representative results from one piglet with the proposed method, where Figs. 3(a) and 3(b) indicate the three consecutively measured PA ID curves and the CO measurement performance, respectively. It can be seen from the results that the proposed noninvasive PA CO method can successfully measure piglet's CO with accuracy comparable with a commercially available invasive system, although further demonstrations are required to achieve complete clinical feasibility of the method. Pooled results with detail descriptions for the *in-vivo* experiment will be shared in a future publication soon [21].

4. Conclusion

In this paper, we theoretically derived and experimentally demonstrated the advanced method of estimating CO, which simultaneously measures composite PA indicator dilution curves generated from both artery and its nearby vein. Because arterial blood vessels for measuring indicator dilution are typically very close to venous ones in most clinical situations, this method has the potential to overcome critical challenges existing on clinical applications of the previously reported PA indicator dilution method. The developed theory indicates that different imaging conditions between the artery and nearby vein, which is common in a clinical situation, don't affect the performance of composite PA indicator dilution curves. Notice that for the derivation of Eq. (9), we considered completely different amounts of hemoglobin and PA conversion factors for the artery and its nearby vein. The concept and feasibility of the composite PA indicator dilution method are verified with *ex-vivo* and *in-vivo* experiments. We expect the approach of composite indicator dilution curves would be the breakthrough of the clinical translation of the combined technology of indicator dilution and PA.

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